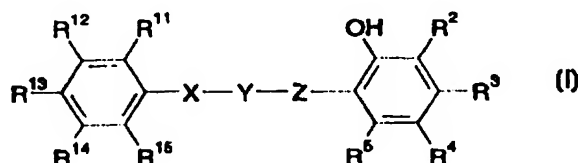




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(54) Title: PHENYL DERIVATIVES USEFUL AS BLOCKERS OF CHLORIDE CHANNELS



(57) Abstract

The present invention relates to a method for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the blockade of chloride channels, comprising administering to a living animal body in need thereof a therapeutically effective amount of a compound having formula (I) or a pharmaceutically acceptable salt thereof wherein R², R³, R⁴ and R⁵ are each independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, amino, and aryl, aralkyl, arylamino, aryloxy, aryl-CO-, or heteroaryl, wherein the aryl or heteroaryl group may be substituted one or more times with substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, hydroxy, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro and amino; or R³ and R⁴ or R⁴ and R⁵ together form a fused 4 to 7 membered carbocyclic ring which may be unsaturated, or partially or fully saturated while the other substituents R², R³, R⁴ and R⁵ is as defined above; Y is -CO-, -CS-, -SO₂-, or -C(=N-R⁸)-, wherein R⁸ is hydrogen, alkyl, or cyano; X is -NH-, -CH₂-NH-, -SO₂-NH-, or -CH₂-; Z is -NR⁶-, -O-, -CH=CH-, -N=CH-, -CH=N-, or -NR⁶-CH₂-, wherein R⁶ is hydrogen, or alkyl; R¹¹, R¹², R¹³, R¹⁴ and R¹⁵ are each independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, amino, and aryl, aralkyl, arylamino, aryloxy, aryl-CO-, or heteroaryl, wherein the aryl or heteroaryl group may be substituted one or more times with substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, hydroxy, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro and amino; or one of R¹¹ and R¹², R¹² and R¹³, R¹³ and R¹⁴ or R¹⁴ and R¹⁵ together form a fused 4 to 7 membered carbocyclic ring which may be unsaturated, or partially or fully saturated while the other substituents R¹¹, R¹², R¹³, R¹⁴ and R¹⁵ is as defined above.

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Phenyl derivatives useful as blockers of chloride channels

The present invention relates to phenyl derivatives which are valuable blockers of chloride channels and as such useful for the treatment of sickle cell anaemia, brain oedema following ischaemia or tumours, diarrhoea, hypertension (diuretic) and for the reduction of the intraocular pressure for the treatment of disorders such as glaucoma. The compounds of the invention may also be useful in the treatment of allergic or inflammatory conditions and for the promotion of wound healing.

Background

Chloride channels serve a wide variety of specific cellular functions and contribute to the normal function of skeletal and smooth muscle cells. Blockers of chloride channels are known to be useful in the treatment of brain oedema following ischaemia or tumours, diarrhoea, hypertension (diuretic) and for the reduction of the intraocular pressure in disorders such as glaucoma.

Sickle cell anaemia and the existence of sickle haemoglobin was the first genetic disease to be understood at the molecular level. The genetic defect underlying sickle cell anaemia causes the substitution of a single amino acid resulting in a mutant haemoglobin, sickle haemoglobin.

The physical manifestations of sickle cell disease is anaemia and painful ischaemic crises due to occlusion of the microcirculation by deformed erythrocytes (sickle cells). The primary cause of sickle erythrocyte deformation and distortion (or sickling) is a reversible polymerisation and gelation of sickle haemoglobin induced at the low oxygen tensions prevalent in metabolically active tissues. Sickle cells are also characterised by an enhanced cation permeability, resulting in cation depletion and cellular dehydration. Since the delay time for the polymerisation has been described as an extremely steep function of the sickle haemoglobin concentration itself, any decrease in cell volume will greatly increase the probability of sickling and thereby of vessel occlusion. Compounds which blocks the deoxygenation induced salt and volume (water) loss may delay the sickling process enough to avoid occlusion upon the passage of the sickle erythrocyte through metabolically active tissue. It has been estimated that a delay time of only 10 sec may suffice.

Several membrane ion channels and transporters present in normal erythrocytes has been suggested to participate in the altered membrane permeabilities of sickle cells. The favoured hypothesis has been stimulation of the Ca^{2+} -activated K^{+} -channel and several blockers of this channel has been suggested as therapeutic agents for the treatment of sickle-cell anaemia (Effects of Cetiedil on Monovalent Cation Permeability in the Erythrocyte: An explanation for the Efficacy of Cetiedil in the treatment of Sickle Cell Anaemia, Berkowitz, L. R., Orringer, E. P., Blood cells, (283-288 (1982) and US patent No. 5.273.992).

Since, K^{+} efflux through a K-channel must be followed by an equal efflux of Cl^{-} to maintain electroneutrality, blockade of erythrocyte chloride channels are predicted to be as effective as blocking the K-channels itself. An advantage to the use of chloride channel blockers is that salt loss which may occur due to activation of unknown K-channel types will indirectly be blocked too.

The compounds according to the invention are valuable blockers of chloride channels as determined by concomitant measurements of conductive netfluxes of chloride and membrane potentials in suspensions of erythrocytes, and the compounds are therefore predicted to be useful in the treatment of ailments responsive to the blockade of chloride channels.

The use of blockers of chloride channels for the treatment of sickle-cell anaemia form a new therapeutic approach.

Several chloride channel blockers and the use thereof have already been described in the technical literature:

Pflügers Arch (1986), 407 (suppl. 2), pages 128-141 describes several compounds with chloride channel blocking activity. A very potent compound described herein is 5-nitro-2-(3-phenylpropylamino)benzoic acid. The reference do not disclose the use of chloride channel blockers for the treatment of sickle cell anaemia.

US patent No. 4.889.612 describes Calixarene derivatives and their use as chloride channel blockers.

US patent No. 4.994.493 describes certain 5-nitrobenzoic acid derivatives and their use in the treatment of cerebral oedema.

WO 96/16647 describes the use of chloride channel blockers for the reduction of the intraocular pressure and specifically the use of chloride channel blockers for the treatment of glaucoma.

Objects of the Invention

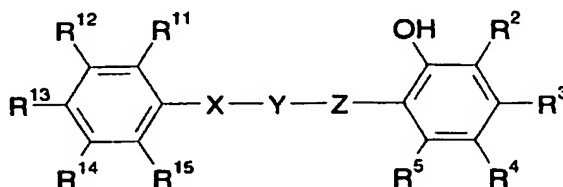
It is an object of the present invention to provide a series of phenyl derivatives and pharmaceutically acceptable salts thereof which are useful for the preparation of a medicament for the treatment of disorders or diseases responsive to the blockade of chloride channels.

Still another object of the present invention is to provide a method of treating disorders or diseases responsive to the blockade of chloride channels, such as for example brain oedema following ischaemia or tumours, diarrhoea, hypertension (diuretic), glaucoma and in particular sickle-cell anaemia. A further object of the present invention is to provide a method for the treatment of allergic or inflammatory conditions and for the promotion of wound healing.

Summary of the Invention

The invention then comprises, inter alia, alone or in combination:

The use of a compound having the formula



or a pharmaceutically acceptable salt thereof

wherein

R^2 , R^3 , R^4 and R^5 are each independently selected from hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; alkoxy; hydroxy; halogen; trifluoromethyl; trifluoromethoxy; cyano; nitro; amino; and aryl, aralkyl, arylamino, aryloxy, aryl-CO-, or heteroaryl, wherein the aryl and heteroaryl groups may be substituted one or more times with substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, hydroxy, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro and amino; and heteroaryl, or R^3 and R^4 or R^4 and R^5 together form a fused 4 to 7 membered carbocyclic ring which may be unsaturated, or partially or fully saturated while the other substituents R^2 , R^3 , R^4 and R^5 is as defined above;

Y is -CO-, -CS-, -SO₂-, or -C(=N- R^8)-, wherein R^8 is hydrogen, alkyl, or cyano;

X is -NH-, -CH₂-NH-, -SO₂-NH-, or CH₂;

Z is -NR⁶-, -O-, -CH=CH-, -N=CH-, -CH=N-, or -NR⁶-CH₂-; wherein R^6 is hydrogen, or alkyl;

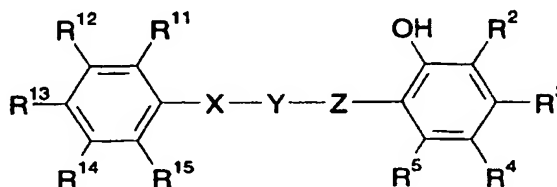
and

R^{11} , R^{12} , R^{13} , R^{14} and R^{15} are each independently selected from hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; alkoxy; hydroxy; halogen; trifluoromethyl; trifluoromethoxy; cyano; nitro; amino; and aryl, aralkyl, arylamino, aryloxy, aryl-CO-, or heteroaryl, wherein the aryl or heteroaryl group may be substituted one or more times with substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, hydroxy, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro and amino; or one of R^{11} and R^{12} , R^{12} and R^{13} , R^{13} and R^{14} or R^{14} and R^{15} together form a fused 4 to 7 membered carbocyclic ring which may be unsaturated, or partially or fully saturated while the other substituents R^{11} , R^{12} , R^{13} , R^{14} and R^{15} is as defined above, for the preparation of a medicament for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the blockade of chloride channels;

the use of a compound as above for the preparation of a medicament for the treatment of sickle-cell anaemia, brain oedema following ischaemia, or tumours, diarrhoea, hypertension (diuretic) and glaucoma;

the use of a compound as above for the preparation of a medicament for the treatment of allergic or inflammatory conditions and ulcers;

a method for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the blockade of chloride channels, comprising administering to a living animal body in need thereof a therapeutically effective amount of a compound having the formula



or a pharmaceutically acceptable salt thereof

wherein

R^2 , R^3 , R^4 and R^5 are each independently selected from hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; alkoxy; hydroxy; halogen; trifluoromethyl; trifluoromethoxy; cyano; nitro; amino; and aryl, aralkyl, arylamino, aryloxy, aryl-CO-, or heteroaryl, wherein the aryl or heteroaryl group may be substituted one or more times with substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, hydroxy, alkoxy, halogen, trifluoromethyl, trifluoromethoxy; cyano, nitro and amino; or R^3 and R^4 or R^4 and R^5 together form a fused 4 to 7 membered carbocyclic ring which may be unsaturated, or partially or fully saturated while the other substituents R^2 , R^3 , R^4 and R^5 is as defined above;

Y is $-CO-$, $-CS-$, $-SO_2-$, or $-C(=N-R^8)-$, wherein R^8 is hydrogen, alkyl, or cyano;

X is $-NH-$, $-CH_2-NH-$, $-SO_2-NH-$, or $-CH_2-$;

Z is NR^6 , O, $-CH=CH-$, $-N=CH-$, $-CH=N-$, or $-NR^6-CH_2-$; wherein R^6 is hydrogen, or alkyl;

R^{11} , R^{12} , R^{13} , R^{14} and R^{15} are each independently selected from hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; alkoxy; hydroxy; halogen; trifluoromethyl;

trifluoromethoxy; cyano; nitro; amino; and aryl, aralkyl, arylamino, aryloxy, aryl-CO-, or heteroaryl, wherein the aryl or heteroaryl group may be substituted one or more times with substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, hydroxy, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro and amino; or one of R¹¹ and R¹², R¹² and R¹³, R¹³ and R¹⁴ or R¹⁴ and R¹⁵ together form a fused 4 to 7 membered carbocyclic ring which may be unsaturated, or partially or fully saturated while the other substituents R¹¹, R¹², R¹³, R¹⁴ and R¹⁵ is as defined above;

a method for the treatment of a disorder or disease of a living animal body which disorder or disease is sickle-cell anaemia, brain oedema following ischaemia, or tumours, diarrhoea, hypertension (diuretic) or glaucoma comprising administering to a living animal body, including a human, in need thereof a therapeutically effective amount of a compound as defined above; and

a method for the treatment of a disorder or disease of a living animal body which disorder or disease is allergic or inflammatory conditions or ulcers comprising administering to a living animal body, including a human, in need thereof a therapeutically effective amount of a compound as above.

Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts such as the hydrochloride, hydrobromide, phosphate, nitrate, perchlorate, sulfate, citrate, lactate, tartrate, maleate, fumarate, mandelate, benzoate, ascorbate, cinnamate, benzenesulfonate, methanesulfonate, stearate, succinate, glutamate, glycollate, toluene-p-sulphonate, formate, malonate, naphthalene-2-sulphonate, salicylate and the acetate. Such salts are formed by procedures well known in the art.

Other acids such as oxalic acid, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts.

Halogen is fluorine, chlorine, bromine or iodine.

Alkyl means a straight chain or branched chain of one to six carbon atoms, including but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and hexyl; methyl, ethyl, propyl and isopropyl are preferred groups.

Cycloalkyl means cyclic alkyl of three to seven carbon atoms, including but not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl;

Cycloalkylalkyl means cycloalkyl as above and alkyl as above, meaning for example, cyclopropylmethyl.

Alkenyl means a group of from two to six carbon atoms, including at least one double bond, for example, but not limited to ethenyl, 1,2- or 2,3-propenyl, 1,2-, 2,3-, or 3,4-butenyl.

Alkynyl means a group of from two to six carbon atoms, including at least one triple bond, for example, but not limited to ethynyl, 1,2-, 2,3-propynyl, 1,2-, 2,3- or 3,4-butyne.

Alkoxy is O-alkyl, wherein alkyl is as defined above.

Amino is NH_2 or NH-alkyl or N-(alkyl)₂, wherein alkyl is as defined above.

Heteroaryl is a 5- or 6-membered heterocyclic monocyclic group. Such a monocyclic heteroaryl group includes, for example, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,5-oxadiazol-3-yl, 1,2,5-oxadiazol-4-yl, 1,2,5-thiadiazol-3-yl, 1,2,5-thiadiazol-4-yl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 1-pyrazolyl, 3-pyrazolyl and 4-pyrazolyl.

Aryl means an aromatic group such as phenyl or naphthyl.

Aralkyl means arylalkyl wherein aryl and alkyl is as defined above, meaning for example benzyl or phenethyl.

I.p. means intraperitoneally, which is a well known route of administration.

P.o. means peroral, which is a well known route of administration.

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

It will be appreciated by those skilled in the art that the compounds of the present invention contain several chiral centres and that such compounds exist in the form of isomers (i.e. enantiomers). The invention includes all such isomers and any mixtures thereof including racemic mixtures.

Some of the compounds of the present invention exist in (+) and (-) forms as well as in racemic forms. Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallization of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example. The compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphoric acid or by the formation of diastereomeric carbamates by reaction of the compounds of the present invention with an optically active chloroformate or the like.

Additional methods for the resolution of optical isomers, known to those skilled in the art may be used, and will be apparent to the average worker skilled in the art. Such

methods include those discussed by J. Jaques, A. Collet, and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

The compounds of the invention may be prepared in numerous ways. The compounds of the invention and their pharmaceutically acceptable derivatives may thus be prepared by any method known in the art for the preparation of compounds of analogous structure, and as shown in the representative examples which follow.

Biology

The compounds of the present invention are potent blockers of chloride channels in normal as well as sickle cell erythrocytes. The ability of the compounds to block the erythrocyte chloride channels could not be demonstrated by classical electrophysiological measurements such as patch clamping, since the channel unit conductance is below the detection limit of these techniques.

All dose-response experiments were therefore performed by concomitant measurements of conductive netfluxes of Cl^- (J_{Cl}) and membrane potentials (V_m) in suspensions of erythrocytes (Bennekou, P. and Christophersen, P. (1986), Flux ratio of Valinomycin - Mediated K^+ Fluxes across the Human Red Cell Membrane in the presence of the Protonophore CCCP. J. Membrane Biol. 93, 221-227.). The membrane Cl^- -conductances were calculated by the following equation (Hodgkin, A. L. and Huxley, A.F. (1952) The components of membrane conductance in the giant axon of loligo. J. Physiol. Lond. 116, 449-472):

$$G_{\text{Cl}} = \frac{F \cdot J_{\text{Cl}}}{(V_m - E_{\text{Cl}})}$$

where F is the Faraday constant and E_{Cl} is the Nernst potential for the Cl^- -ion.

Administration of N-(3-Trifluoromethylphenyl)-N'-(2-hydroxy-3-nitro-phenyl) urea to a suspension of normal erythrocytes blocked G_{Cl} more than 95 % with an IC_{50} -value of 4 μM . The compound equipotently blocked G_{Cl} from oxygenated as well as deoxygenated homozygoteous sickle cell erythrocytes.

Pharmaceutical compositions

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides pharmaceutical formulations comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, subcutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Formulations containing ten (10) milligrams of active ingredient or, more broadly, 0.1 to one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the

following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more

emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, formulations adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

Methods of treating

The compounds of the present invention are, due to their potent chloride channel blocking activity, useful in the treatment of sickle cell anaemia, brain oedema following ischaemia or tumors, diarrhoea, and hypertension (diuretic) as well as other disorders responsive to the blockade of chloride channels. The compounds of the invention may also be useful in the treatment of allergic and inflammatory conditions, for the promotion of wound healing and the treatment of ulcers. The compounds of the present invention may accordingly be administered to a living animal body, including a human, in need of treatment, alleviation, or elimination of an indication associated with or responsive to chloride channel blocking activity. This includes especially sickle cell anaemia, brain oedema following ischaemia or tumors, diarrhoea, and hypertension (diuretic).

Suitable dosage range are 0.1-500 milligrams daily, and especially 10-70 milligrams daily, administered once or twice a day, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

The following examples will illustrate the invention further, however, they are not to be construed as limiting.

EXAMPLE 1**N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-nitrophenyl) urea**

2-hydroxy-5-nitroaniline (1.25 g, 8.1 mmol) and 3-(trifluoromethyl)phenyl isocyanate (1.00 ml, 7.3 mmol) were added to toluene (50 ml). The reaction mixture was stirred at RT overnight, the product filtered off and recrystallized from methanol/water 8:1 (45 ml). 1.39 g (56%) of the title compound was isolated. M.p. 226°C (dec.).

The following compounds were prepared in a similar manner:

N-(3-(trifluoromethyl)phenyl)-N'-(2, 5-dimethoxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-4-(phenylamino)phenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitrophenyl) urea. M.p. 199-200°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea. M.p. 171-173°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-tert-butylphenyl) urea. M.p. 173-174°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxyphenyl) urea. M.p. 153-154°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-5-(trifluoromethyl)phenyl) urea. M.p. 192-194°C,
N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-naphthyl) urea. M.p. 184-188°C (dec.),
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-1-naphthyl) urea. M.p. 187-189°C (dec),
N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-5-chlorophenyl) urea. M.p. 169-171°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-nitrophenyl) urea. M.p. 174-175°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxyphenyl) urea. M.p. 178-179°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2, 5-dimethoxy-4-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-3-nitrophenyl) urea. M.p. 223-224°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-chlorophenyl) urea. M.p. 173-174°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-5-methoxycarbonyl-4-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chloro-4-nitrophenyl) urea. M.p. 201-203°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-5-methoxycarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-4-nitro-5-carboxyphenyl) urea.

EXAMPLE 2**N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-aminophenyl) urea.**

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitrophenyl) urea (1.00 g, 2.9 mmol) was subjected to catalytic reduction in tetrahydrofuran (50 ml) using 5% palladium on carbon (0.20 g). The reaction mixture was filtered through a path of celite. Evaporation of the filtrate and subsequent recrystallization of the crude product from methanol/water 1:1 (50 ml) afforded the title compound. 0.68 g (75%) of the title compound was isolated. M.p. 200-202°C.

EXAMPLE 3**N-(1-naphthyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea.**

2-hydroxy-5-(trifluoromethyl)aniline (0.12 g, 0.7 mmol) in toluene (3 ml) was added to a solution of alpha-naphthyl isocyanate (0.11 g, 0.7 mmol) in toluene (3 ml). The reaction was stirred at RT overnight and the product filtered off. 0.17 g (72%) of the title compound was isolated. M.p. 205-207°C.

EXAMPLE 4**N-(2-methoxy-5-chlorophenyl)-3-(trifluoromethyl)phenylacetic amide.**

Dicyclohexylcarbodiimide (2.20 g, 10.7 mmol) was added to a solution of 3-(trifluoromethyl)phenylacetic acid (2.00 g, 9.8 mmol) and 5-chloro-2-methoxyaniline (1.55 g, 9.8 mmol) in dichloromethane (50 ml). The reaction was stirred at RT overnight. The reaction mixture was filtered and the filtrate evaporated to dryness. The residue was recrystallized from methanol/water 2:1 (30 ml). 2.05 g (61%) of the title compound was isolated.

The following compound was prepared in a similar manner.

N-(3-(trifluoromethyl)phenyl)-2-methoxy-5-chlorophenylacetic amide starting from 3-trifluoromethylphenylamine and 2-methoxy-5-chlorophenylacetic acid.

EXAMPLE 5**N-(3,5-dichlorophenyl)-N'-(2-methoxy-5-(trifluoromethyl)phenyl) urea**

3,5-dichlorophenyl isocyanate (0.94 g, 5.0 mmol) in toluene (10 ml) was added to a solution of 2-methoxy-5-(trifluoromethyl)aniline (0.96 g, 5.0 mmol) in toluene (10 ml). The reaction was stirred at RT for 1 hour and the product filtered off. 1.20 (63%) of the title compound was isolated.

EXAMPLE 6**N-(5,6,7,8-tetrahydro-1-naphthyl)-N'-(2-methoxy-5-(trifluoromethyl)phenyl) urea.**

2-methoxy-5-(trifluoromethyl)phenyl carbamoylchloride (0.81 g, 3.2 mmol), 1-amino-5,6,7,8-tetrahydronaphtalene (445 ml, 3.2 mmol) and triethylamine (446 ml, 3.2 mmol) were added to chloroform (20 ml) and the resulting mixture was stirred at RT overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The solvent was evaporated in vacuo and the residue recrystallized from toluene (20 ml). 0.45 g of the title compound was isolated.

EXAMPLE 7**N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-5-(trifluoromethyl)phenyl) thiourea.**

3-(trifluoromethyl)phenyl isothiocyanate in toluene (0.76 ml, 5.0 mmol) was added to a solution of 2-methoxy-5-(trifluoromethyl)aniline in toluene (10 ml). The resulting reaction mixture was stirred at RT overnight and the product was subsequently filtered off. 1.00 g (51%) of the title compound was isolated.

The following compound was prepared in a similar manner.

N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-5-chlorophenyl) thiourea.

EXAMPLE 8**N-(3-methoxycarbonylphenyl)-N'-(2-methoxy-5-chlorophenyl) urea.**

N-(3-carboxyphenyl)-N'-(2-methoxy-5-chlorophenyl) urea (3.00 g, 9.4 mmol) was suspended in methanol (100 ml). Concentrated sulfuric acid (1.0 ml) was added and the reaction was heated at reflux for 6 hours. The reaction mixture was poured into cold (0°C) water (600 ml). Filtration of the suspension afforded the crude product. The crude product was purified by column chromatography on silica using dichloromethane/ethyl acetate 19:1 as eluent. 2.35 g of the title compound was isolated.

EXAMPLE 9**1-(3-(trifluoromethyl)phenyl)-3-(2-methoxy-5-chlorophenyl) guanidine.**

A mixture of 3-(trifluoromethyl)phenylcyanamide (2.00 g, 10.7 mmol) and 5-chloro-2-methoxyaniline hydrochloride (2.30 g, 11.8 mmol) was suspended in acetonitrile (80 ml). The reaction was heated at reflux for four days. The solvent was evaporated in vacuo. The residue was redissolved in dichloromethane (100 ml) and washed with a saturated sodium bicarbonate solution. The crude product was purified by column chromatography on silica gel initially using dichloromethane as eluent followed by dichloromethane/methanol 9:1 as eluent. 2.27 g of the title compound was obtained as a dark oil which slowly crystallises.

EXAMPLE 10**N-(3-benzoylphenyl)-N'-(2-methoxy-5-chlorophenyl) urea.**

A mixture of 5-chloro-2-methoxyphenyl isocyanate (1.00 g, 5.4 mmol) and 3-aminobenzophenone (1.29 g, 6.5 mmol) was stirred in toluene (20 ml) for two days. The reaction was filtered and the filter cake washed with toluene. 1.9 g of the title compound was isolated.

The following compounds were prepared in a similar manner.

N-(3-carbamoylphenyl)-N'-(2-methoxy-5-chlorophenyl) urea,
N-(3-(trifluoromethoxy)phenyl)-N'-(2-methoxy-5-chlorophenyl) urea,
N-(3-methylphenyl)-N'-(2-methoxy-5-chlorophenyl) urea,
N-(3-hydroxyphenyl)-N'-(2-methoxy-5-chlorophenyl) urea,
N-(3-nitrophenyl)-N'-(2-methoxy-5-chlorophenyl) urea, and
N-(3-carboxyphenyl)-N'-(2-methoxy-5-chlorophenyl) urea.

EXAMPLE 11

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-(phenylamino)phenyl) urea

To a cold (0°C) suspension of N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-4-(phenylamino)phenyl) urea (1.00 g, 2.5 mmol) in dichloromethane (50 ml), boron tribromide (0.48 ml, 5.1 mmol) was added. After the addition of boron tribromide the ice bath was removed and the reaction mixture was stirred for 3 hours at RT. The reaction was poured on ice (10 ml) and 1 M sodium bicarbonate (50 ml) was added. The aqueous phase was extracted with ethyl acetate (50 ml) and the organic phase dried over magnesium sulfate. 1.05 g crude product was obtained. The crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate 1:1 as eluent. The partly purified product (0.61 g) was recrystallized from ethanol/water 1:1 (20 ml). 0.20 g (21%) of the title compound was isolated. M.p. 166-168°C.

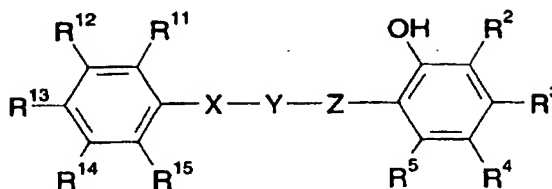
The following compounds were prepared in a similar manner.

N-(3-(trifluoromethyl)phenyl)-N'-(2, 5-dihydroxyphenyl) urea, M.p. 165-168°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea, M.p. 160-162°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorobenzyl) urea, M.p. 56-66°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2,3-dihydroxybenzyl) urea, M.p. 159-161°C,
N-(2-hydroxy-5-chlorophenyl)-3-(trifluoromethyl)phenylacetic amide, M.p. 148-153°C,
N-(3, 5-dichlorophenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea, M.p. 202°C,
N-(5,6,7,8-tetrahydro-1-naphthyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) thiourea, M.p. 124-125°C,
N-(3-methylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, M.p. 179-180°C,
N-(3-hydroxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-nitrophenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, M.p. 194-196°C,
N-(3-benzoylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, M.p. 205-206°C,
N-(3-(trifluoromethoxy)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, M.p. 158-159°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxy-4-nitrophenyl) urea, M.p. 220-222°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2, 4-dihydroxyphenyl) urea, M.p. 179-180°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxyphenyl) urea, M.p. 176-177°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) thiourea,
1-(3-(trifluoromethyl)phenyl)-3-(2-hydroxy-5-chlorophenyl) guanidine, M.p. 172-174°C,
and
N-(3-(trifluoromethyl)phenyl)-2-hydroxy-5-chlorophenylacetic amide, M.p. 148-150°C.

We Claim:

1. The use of a compound having the formula



or a pharmaceutically acceptable salt thereof

wherein

R², R³, R⁴ and R⁵ are each independently selected from hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; alkoxy; hydroxy; halogen; trifluoromethyl; trifluoromethoxy; cyano; nitro; amino; and aryl, aralkyl, arylamino, aryloxy, aryl-CO-, or heteroaryl, wherein the aryl and heteroaryl groups may be substituted one or more times with substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, hydroxy, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro and amino; or R³ and R⁴ or R⁴ and R⁵ together form a fused 4 to 7 membered carbocyclic ring which may be unsaturated, or partially or fully saturated while the other substituents R², R³, R⁴ and R⁵ is as defined above;

Y is -CO-, -CS-, -SO₂-, or -C(=N-R⁶)-, wherein R⁶ is hydrogen, alkyl, or cyano;

X is -NH-, -CH₂-NH-, -SO₂-NH-, or CH₂;

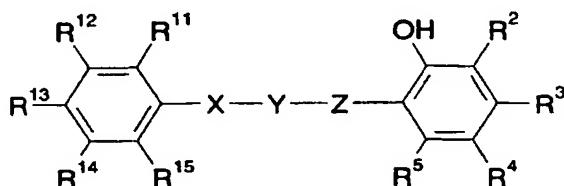
Z is -NR⁶-, -O-, -CH=CH-, -N=CH-, -CH=N-, or -NR⁶-CH₂-, wherein R⁶ is hydrogen, or alkyl;

and

R¹¹, R¹², R¹³, R¹⁴ and R¹⁵ are each independently selected from hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; alkoxy; hydroxy; halogen; trifluoromethyl; trifluoromethoxy; cyano; nitro; amino; and aryl, aralkyl, arylamino, aryloxy, aryl-CO-, or heteroaryl, wherein the aryl or heteroaryl group may be substituted one or more times

with substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, hydroxy, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro and amino; or one of R^{11} and R^{12} , R^{12} and R^{13} , R^{13} and R^{14} or R^{14} and R^{15} together form a fused 4 to 7 membered carbocyclic ring which may be unsaturated, or partially or fully saturated while the other substituents R^{11} , R^{12} , R^{13} , R^{14} and R^{15} is as defined above, for the preparation of a medicament for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the blockade of chloride channels.

2. The use of a compound according to claim 1 for the preparation of a medicament for the treatment of sickle-cell anaemia, brain oedema following ischaemia, or tumours, diarrhoea, hypertension (diuretic) and glaucoma.
3. The use of a compound according to claim 1 for the preparation of a medicament for the treatment of allergic or inflammatory conditions and ulcers.
4. A method for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the blockade of chloride channels, comprising administering to a living animal body in need thereof a therapeutically effective amount of a compound having the formula



or a pharmaceutically acceptable salt thereof

wherein

R^2 , R^3 , R^4 and R^5 are each independently selected from hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; alkoxy; hydroxy; halogen; trifluoromethyl; trifluoromethoxy; cyano; nitro; amino; and aryl, aralkyl, arylamino, aryloxy, aryl-CO-, or heteroaryl, wherein the aryl or heteroaryl group may be substituted one or more times with substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, hydroxy, alkoxy, halogen, trifluoromethyl, trifluoromethoxy; cyano, nitro and amino; or R^3 and R^4 or R^4 and R^5 together form a fused 4 to 7 membered carbocyclic ring which may be

unsaturated, or partially or fully saturated while the other substituents R^2 , R^3 , R^4 and R^5 is as defined above;

Y is $-\text{CO}-$, $-\text{CS}-$, $-\text{SO}_2-$, or $-\text{C}(=\text{N}-\text{R}^6)-$, wherein R^6 is hydrogen, alkyl, or cyano;

X is $-\text{NH}-$, $-\text{CH}_2\text{-NH}-$, $-\text{SO}_2\text{-NH}-$, or $-\text{CH}_2-$;

Z is $-\text{NR}^6-$, $-\text{O}-$, $-\text{CH}=\text{CH}-$, $-\text{N}=\text{CH}-$, $-\text{CH}=\text{N}-$, or $-\text{NR}^6\text{-CH}_2-$, wherein R^6 is hydrogen, or alkyl;

R^{11} , R^{12} , R^{13} , R^{14} and R^{15} are each independently selected from hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; alkenyl; alkynyl; alkoxy; hydroxy; halogen; trifluoromethyl; trifluoromethoxy; cyano; nitro; amino; and aryl, aralkyl, arylamino, aryloxy, aryl-CO-, or heteroaryl, wherein the aryl or heteroaryl group may be substituted one or more times with substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, hydroxy, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro and amino; or one of R^{11} and R^{12} , R^{12} and R^{13} , R^{13} and R^{14} or R^{14} and R^{15} together form a fused 4 to 7 membered carbocyclic ring which may be unsaturated, or partially or fully saturated while the other substituents R^{11} , R^{12} , R^{13} , R^{14} and R^{15} is as defined above.

5. A method for the treatment of a disorder or disease of a living animal body which disorder or disease is sickle-cell anaemia, brain oedema following ischaemia, or tumours, diarrhoea, hypertension (diuretic) or glaucoma comprising administering to a living animal body, including a human, in need thereof a therapeutically effective amount of a compound according to claim 4.

6. A method for the treatment of a disorder or disease of a living animal body which disorder or disease is allergic or inflammatory conditions or ulcers comprising administering to a living animal body, including a human, in need thereof a therapeutically effective amount of a compound according to claim 4.

INTERNATIONAL SEARCH REPORT

Inter nat Application No
PCT/EP 97/02724

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/17 A61K31/235 A61K31/24 A61K31/165 A61K31/155
A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94 22807 A (NEUROSEARCH AS ;OLESEN SOEREN PETER (DK); MOLDT PETER (DK); PEDERS) 13 October 1994 see claims; examples ---	1,2,4,5
Y	US 5 234 922 A (WELSH MICHAEL J ET AL) 10 August 1993 see column 5, line 5 - line 8; claims 1,6 --- -/--	1,2,4,5

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

2

Date of the actual completion of the international search 19 August 1997	Date of mailing of the international search report 29. 08. 97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Authorized officer Seufert, G

INTERNATIONAL SEARCH REPORT

Inter. Application No
PCT/EP 97/02724

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 107, no. 11, 14 September 1987 Columbus, Ohio, US; abstract no. 89293, WANGEMANN, P. ET AL: "Chloride - channel blockers in the thick ascending limb of the loop of Henle. Structure-activity relationship" XP002038036 cited in the application see abstract & PFLUEGERS ARCH. (1986), 407 (SUPPL. 2), S128-S141, ---	1-6
A	WO 96 08242 A (CHILDRENS MEDICAL CENTER) 21 March 1996 see claims -----	1-6

INTERNATIONAL SEARCH REPORT

national application No.

PCT/EP 97/ 02724

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 4-6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter: .nal Application No

PCT/EP 97/02724

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9422807 A	13-10-94	AU 6537894 A CA 2160128 A EP 0693053 A FI 954746 A JP 8510448 T NO 953956 A	24-10-94 13-10-94 24-01-96 17-11-95 05-11-96 07-12-95
US 5234922 A	10-08-93	NONE	
WO 9608242 A	21-03-96	AU 3634795 A EP 0781128 A	29-03-96 02-07-97

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